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REPORT OF THE
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Acute Lobar Pneumonia. During the quarter forty-three patients suffering from acute lobar pneumonia have been admitted to the Hospital. This number is somewhat larger than the number admitted during the same period last year. Of these patients ten were due to pneumococci of type I. All the patients of this type were treated and all recovered. No observations have been made to change our former conclusions as to the efficacy of serum of type I. in cases due to type I infection. During the present winter only a part of the cases due to type II have been treated with immune serum. The results have not been satisfactory. There has been no evidence that the serum has had any very marked effect. At the present time we are not treating cases due to this type of organism with immune serum.

Small amounts of the serum of type I have been sent to the Brigham Hospital in Boston, the Presbyterian Hospital in New York, and to Dr Hanes of Richmond. Reports on the results obtained have not yet been received. If the type I serum is to be sent out and to be used more or less indiscriminately, an important question is as to the use of preservatives. No preservatives have been employed in any of the serum so far used. It is obvious that the use of such serum is accompanied by considerable danger. Considerable study will have to be made to determine whether the use of a preservative is practical, where such large amounts of serum are administered. A practical method of concentration of the serum would, to some extent overcome the difficulties. The study of methods of concentration by Dr Avery and by Dr Gay and Dr Chickering has been of great theoretical interest, but, so far, these studies do not seem to be of practical application. The method employed by Dr Avery requires very extensive handling of the serum, with corresponding danger of contamination, and a concentration of only about four times is obtained. The concentration of serum by the method described by Dr Gay and Dr Chickering has demonstrated the

ability of obtaining the immune bodies in very small amounts of protein, but the results so far, owing to unknown factors, cannot be constantly obtained, and in many cases where such results are obtained there is considerable loss in the immune substance, so that the method practically would be very expensive. Important principles, however, have been demonstrated by these investigations and it is quite possible that practical application may be made of them. The important fact, however, has been determined now beyond any doubt that the limit to the practical application of this form of therapy is dependent upon the degree of infection. If the infection is of a certain type, no amount of immune serum will protect, and concentration of immune bodies is of no practical advantage. Observations which we have made, however, indicate that, if the concentration of immune bodies in a given serum may not furnish better protection than is obtained by the unconcentrated serum, it may be possible to produce a higher grade of protection, possibly depending upon the so-called avidity of the immune bodies for the bacteria.

The therapeutic treatment of cases of type I now seems to have reached a practical stage, while the treatment of pneumonia due to other types is still in a purely experimental condition. The New York Board of Health is now preparing serum of type I and serum of type I is being prepared by Dr Lewis at the Phipps Institute, Philadelphia. Commercial houses have desired our co-operation in the preparation of serum but we have discouraged their taking up this matter at the present time. A more detailed account of the exact nature of the work on pneumonia follows.

Observations dealing with the occurrence of pneumococci of various types in the mouths of healthy persons, and in those of persons sick and convalescent from pneumonia are being constantly carried on by Dr Dochez and Dr Avery. Twenty families in which one or more members have been sick of pneumonia have been quite thoroughly studied. In eight of these families one or more healthy members have been discovered to be carriers of pneumococci of a fixed type. In all the so-called carriers so far determined the type of organism has been the same as that responsible for the case of

pneumonia in the family. These carriers have been followed wherever possible until the fixed virulent type of pneumococcus disappeared from the sputum. The longest period during which healthy persons have so far been found to carry the fixed type of organism has been forty days; the shortest twenty-one days; the average approximately thirty days. In none of these carriers that have been observed has pneumonia developed. Three instances of pneumococcus infection occurring in individuals in contact with cases of pneumonia, however, have been observed and studied. In each case the type of organism isolated corresponded to the type found in the case considered as the source of infection. Further studies have been made concerning the length of time during convalescence, during which patients with pneumonia harbour in their mouths the fixed virulent types of pneumococci. The longest period during which the patient has carried the pneumococcus of the fixed type has been ninety days, and the shortest period has been twelve days; the average has been about twenty-nine days.

Studies concerning the mode of action of antipneumococcus serum are being made. Dr Avery has shown that when a mixture of pneumococci and anti-pneumococcus serum is made no bacteriolytic or bactericidal action could be observed. When, however, plates are made from the mixture at short intervals of time, there can be demonstrated a well-defined inhibition of growth during a period of about six hours. This retardation of growth is not dependent upon agglutination, since it may occur in dilutions of serum in which no agglutination of the organism occurs, and it is not completely specific for the different types, while agglutination, on the other hand, is very specific. This phenomenon has suggested that part of the action of the serum may be due to inhibition of certain metabolic activities of the bacteria. We had previously found that immune serum when mixed with pneumococci did not inhibit the power of the latter to produce methemoglobin. Later observations, however, have shown that if the bacteria and serum are allowed to remain in contact with one another at 37°C for two hours before the hemoglobin is added, no methemoglobin formation occurs, so that the serum apparently does possess the power of inhibiting this functional activity of pneumococci.

Dr Dechez and Dr Avery are making observation to determine whether or not the serum inhibits certain digestive and fermentative properties of the pneumococcus, especially the formation of amino acid from protein, and the fermentation of various carbohydrates. It has been found that when the normal curves of these types of activity have been determined, when immune serum is added to comparable mixtures there is either complete or partial inhibition. It is possible, therefore, that a part of the action of immune serum may be due to the inhibition of fermentative processes, which bacteria carry on in the medium immediately surrounding them, which processes are necessary for the life of the bacteria. Experiments indicate, however, that the inhibition of these activities of the pneumococci are not absolutely specific as regards sera of the different types in relation to the corresponding organisms.

Dr Avery has made a study of the relationship of the fermentative reactions of the different types of pneumococci to the antigenic differences. A large number of strains of the different types have been studied, but no well-defined differences in the fermentative activity of the members of the different groups could be determined.

Dr Chickering has continued the work commenced by him and Dr Gay on the specific precipitation of antibodies from antipneumococcus serum by bacterial extracts. Their conjoint work has already been published. Various methods of producing the bacterial extracts have been tried, but the use of large amounts of acetone as employed by Dr Van Slyke and others in the precipitation of ferments, has proved to be of the greatest value. Dried acetone-precipitated bacterial substances go into solution much more easily than the bacterial substances prepared in other ways. The fractional employment of bacterial extracts in the precipitation of immune serum has been found to be effective in completely removing the protective substances from the serum. To remove the bacterial protein from the serum precipitate, the best method has been found to consist in extracting the precipitate with normal saline, after the addition of weak alkalis, as sodium carbonate, heating and shaking. The supernatant fluid after centrifugalization contains only a very small amount of protein and apparently protects

animals as well as the whole serum. Such extracts not only contain the protective substance, but also agglutinin and precipitins. Studies have been carried on to determine the toxicity of the extracts in various animals, under various conditions. No administration of such extracts has yet been made to patients, but the experiments indicate that there is little danger of their producing toxic effects. Studies have also been made to determine the duration of the immunity following the administration of extracts, and also the possibility of producing slight active, as well as passive, immunity, by means of such extracts. Apparently passive immunity, whether obtained by whole serum or precipitates, has disappeared at the end of about five days, but after ten days when the extracts are used slight grades of active immunity are seen.

Studies are being carried on by Dr Cole with the assistance of Miss Stryker which have for their objects first, the determination of the difference between active and passive pneumococcus immunity, and secondly, the production of more effective immune serum. By careful qualitative studies in mice it has been found that by the production of very slight grades of active immunity the degree of effect obtained from immune serum is very markedly increased, much more markedly than can be accounted for by a simple addition of the two factors. Second, by treating animals with daily doses of living bacteria, combining these doses of bacteria with an amount of immune serum sufficient to protect the animal, it has been found possible to produce within three or four weeks such immunity in rabbits that the serum will protect mice against doses of virulent culture as high as 1 to 1.5 c.c., whereas horse serum, obtained by the ordinary method of immunization, even after six months, or even after one year's treatment, is able to protect against no more than .1 or at most .2 c.c. of virulent culture. A goat is now in process of immunization, and if the serum of this animal proves efficacious, we shall proceed with the immunization of horses by this new method.

Dr. Cohn. Heart Disease.

It is generally believed that the form of the electrocardiogram remains constant in human beings for long periods of time. In experiments on animals it has been

found that its form can be altered by the application of heat to the apex or base of the ventricle, by the application of muscarin to the surface of the heart, and by the stimulation of the vagus nerve. In studying the curves of patients to whom digitalis is given we have found that under the influence of this drug the form of the electrocardiogram is also changed. The change takes place in that part of the curve included between the R and the end of the T wave. The T wave flattens and later becomes inverted in the greater number of our patients. It is a general rule that inversion of the T wave depends on the fact that the apical portions of the ventricular muscle are, relatively, electrically more active than the base. Digitalis evidently has the power of bringing about this state. We have discovered this effect of digitalis in a day and a half to two days after beginning the administration by mouth. It outlasts the administration by five to twenty-two days. If the presence of the electrical change actually means that the drug is still present in the heart muscle, it becomes clear why digitalis action in patients comes on so promptly when a second course of treatment is begun ten days after the first ended, for after so long a period complete elimination is usually believed to have taken place.

We have utilized this sign of change in T waves in studying the question of stimulation of failing hearts in pneumonia. In pneumonia, especially among acute infections, the value of digitalis as a stimulant has been much debated. The first point we thought, which should be decided, was whether there was a way of determining that digitalis was exerting an influence. It was clear, from our own and from the experiences of others, that to judge by its effect on the rate of the heart was valueless. We found in the electrocardiograms of pneumonia patients what the T wave changed just as it does in the non-febrile. The change takes place in about the same length of time, and it requires about the same amount of the drug to produce it. We have, therefore, a means of telling that digitalis does produce an effect. In the group of patients who develop auricular flutter or fibrillation, a rhythm of the heart, which develops spontaneously in pneumonia, digitalis is beneficial. The rate of the heart, when

these rhythms occur, usually rises to a great height. Digitalis has the power of reducing the ventricular rate in them, by blocking the auricular impulses, just as it does in non-febrile patients having these rhythms. Whether it is beneficial when the rhythms is normal, we are not yet able to say.

Dr Jamieson has attempted in another way to find whether there is a difference between the action of digitalis in pneumonia and the non-febrile state. He injected crystalline strophanthin(ouabaine) intravenously into dogs and cats, to find the minimal lethal dose per kilogram. In this he followed the method of Hatcher and Eggleston. Then he injected a number of dogs and cats with virulent cultures of pneumococci by the method of insufflation. When the animals were at the height of the disease, he injected strophanthin into them in the same way as in the control. He found that the minimal lethal dose per kilogram was the same in the infected as in the non-infected animals, 0.1 mgm. in cats and 0.12 mgm. in dogs. Post mortem the lungs of the animals were seen to be consolidated,

The conclusion is drawn from the observations in patients and from the experiments in infected animals, that digitalis or strophanthin, may be expected to act in the same way.

Dr Cohn carried out experiments, some time ago, in dogs which showed certain quite definite differences between the action of the right and the left vagus nerves. The main difference was that stimulation of the right acted more especially on the pace-maker, while stimulation of the left acted more especially on auriculo-ventricular conduction. Experiments were next carried out to see what influence the sino-auricular node, usually accepted as the pace-maker of the heart, exerted on this difference. The sinus node was therefore destroyed in the jaws of a clamp. It was found that stimulating the vagus nerve still showed about the same differences as before, except that stimulating the left vagus nerve caused a greater effect on the pace-making function than it did before destroying the node. This effect differed in that, before clamping, the auricles continued to beat during stimulation, after clamping they ceased. It appeared, therefore, that an influence which caused the

nerve fibers to continue to contract during left vagus stimulation had been destroyed. The attempt was therefore made to discover whether the accelerators provided this stimulus. These were accordingly cut in a number of experiments, sometimes the right, sometimes the left, and sometimes both. Cutting them produced no influence on the usual difference between the vagus nerves. What mechanism it is which is affected when the S-A node is destroyed, has not yet been ascertained.

The study of the action of digitalis in patients suffering from heart disease is being continued. The action of the drug is being studied on rate of the beats, on conduction, blood pressure, diuresis, and its effect on the electrocardiogram. Former reports have dealt with its action in patients having simple forms of disease. We are now collecting data in more complicated forms in which abnormal rhythms, high blood pressure, oedema, and dyspnoea are found. Experiments in animals are going on, planned to correlate the changes which take place in the size, shape and weight of the heart under various conditions with the electrocardiographic curves. The shape and size are determined by X-ray observation - the weight, post mortem. These animals are to be studied under the condition of strain, as when dogs run on the tread-mill, and also in the presence of artificial valvular lesions. The influence of digitalis on them is also to be studied.

Study of Diabetes.

Up to the present time forty-one patients with diabetes have been treated in this hospital. The results of treatment of patients, up to the present, are as follows: Total number of patients treated, forty-one. Number of deaths, five. Of these, two were deaths in coma shortly after entering the hospital; one patient with a severe cardiac lesion died of heart failure, shortly after entering the hospital; one boy died following a break in diet; one man recently died after several months of decline in spite of treatment, and autopsy showed caseous (tubercular) pneumonia. Two other patients treated in coma were brought out of coma. Of several others received close to coma, none went into coma. Two patients have left the hos-

without permission or instructions, after several months of treatment and improvement. (One of these left because he imagined himself well.) Twenty patients have been discharged in satisfactory condition, free from glycosuria and acidosis. Several of these were children, ranging from seven to seventeen years of age. Two patients have been discharged owing to breaking diet, but have re-entered the hospital in better condition than at first, and have been cleared up more easily than at first. One other patient has had a slight relapse owing to the advice of another physician that he eat bread. Other patients' reports show continued freedom from glycosuria or symptoms. This includes Mr. Weststreet, the first patient, whose case was one of the severest. The remaining patients in the hospital are kept sugar-free and apparently improving.

The routine study of these patients, involving as it does a very large number of chemical analyses of urine, requires much time and labour. Under the section "Reports from the Chemical Laboratory" is given a description of the studies of acidosis which are being made.

Dr Stillman is also studying the blood sugar in a series of cases, especially with reference to the relation between the concentration of sugar in the blood and rate of excretion in the urine.

As will be remembered, the theoretical basis of the treatment employed is that pancreatic function may be spared by diminishing body mass and metabolic activity. This was based on the changes observed in depancreatized animals, under varying conditions. The studies in animals are being continued, parallel to the studies in patients. Partially depancreatized animals are being subjected to conditions which alter body mass or metabolic activity. It is hoped by such observations to obtain evidence in support of the theoretical deductions on which the treatment is based.

Dr Allen has previously brought experimental evidence in favour of the view that blood sugar exists in a different physical state in diabetic and non-diabetic animals. Experiments are now under way and observations are being made having for their purpose the demonstration of such physical differences.

The study of morphological changes in the Islands of Langerhans occurring in diabetic animals and in patients is being continued. The large amount of material in all stages of the disease, as well as of fresh human material, affords exceptional opportunity for the study of this problem.

It is now planned during the summer to publish the material so far obtained in the form of a monograph. This will include (a) a report of the animal experiments to form the basis for the proposed modification in the treatment of diabetes; (b) a description of the method of treatment and reports of clinical cases treated.

Studies concerning the Nature of Acidosis and especially Acidosis in Diabetes

Dr Van Slyke, Dr Stillman and Mr Cullen have undertaken a study of acidosis in diabetes. Preliminary work by Dr Van Slyke and Dr Stillman has indicated that the determination of the carbon dioxide tension of the alveolar air is one of the most reliable methods, if not the most valuable method, of determining the actual condition of the patient, as regards acidosis. A very large number of observations of alveolar CO₂ tension in the patients with diabetes has been made by Dr Stillman, by a method which is quite simple, but seems to yield accurate and comparable results, at least in patients not comatose, and who can be taught a very simple procedure. Dr Van Slyke and Mr Cullen then undertook the problem of determining the changes in the blood which corresponds to the changes in alveolar carbon dioxide, in order that the interpretation of the latter determinations might be put on a firm scientific basis. Mr Cullen has gone on with the work commenced by Dr Zacharias last year, the direct determination of hydrogen ion concentration in the blood by electrometric methods, and has developed the method for the present purpose. It had already been shown by Haeussler and others that in acidosis the actual hydrogen ion concentration of the blood undergoes little or no change and Mr Cullen has confirmed these observations. It then seemed that it might be possible to determine by this method whether or not the reserve alkalinity of the blood in such cases was decreased. To determine this two methods have been employed and by these methods it has been possible to determine that such de-

crease in reserve alkalinity is actually present. First, when a given amount of HCl is added to the plasma of a case of acidosis, the acidity developed, as measured by the hydrogen ion concentration with the electrometric method, is much greater than when normal plasma is treated in the same way. As an example of results, the hydrogen ion concentration obtained after adding one volume of $\frac{N}{50}$ HCl to the plasma from a severe case of acidosis was one hundred and fifty times as great as the hydrogen ion concentration of normal plasma similarly treated.

Second, Dr Van Slyke has been able to show that the ability of the plasma to fix carbon dioxide which, of course, depends on the amount of reserve alkalie, in such forms as alkaline phosphate and carbonate, is reduced in acidosis. In order to demonstrate this fact, it has been necessary to develop a method, which has been simplified so as to render accurate and frequent determinations possible. The method in principle, is as follows:

The plasma is shaken for about a minute with air containing approximately 6% of CO₂ (This is obtained by blowing the shaking vessel full of alveolar air from the lungs). The plasma under these conditions dissolves mechanically five per cent of its volume of CO₂ and by virtue of its alkalinity combines chemically with a great deal more. Normal serum fixes seventy five per cent of its volume of CO₂. In acidosis the reserve alkalinity of the blood may be so far reduced that the CO₂ capacity falls to twenty per cent. For estimation of the combined CO₂ a simple one-piece apparatus has been devised, which permits a determination to be made in about three minutes, the CO₂ gas removed from one c.c. of plasma being read directly on a scale. The apparatus consists essentially of a fifty c.c. pipette closed above and below by stoppers and connected below with a levelling bulb full of mercury. The pipette is completely filled with mercury. Then one c.c. of plasma and a few drops of acid, to free the combined CO₂, are introduced through the upper stop cock. The pipette is then evacuated by merely lowering the levelling bulb below the height of a barometric column. The plasma, left in the evacuated pipette, is shaken for a few seconds

as the result of which the CO_2 gas immediately leaves the solution. The mercury is then let back into the pipette, and the volume of CO_2 read off on the upper stem, on which a scale is etched. Duplicate results rarely vary by more than one per cent.

Normal plasma binds 75 per cent of its volume of CO_2 . In cases of acidosis the figure may be as low as 20 per cent. This new and simple technique for determining the CO_2 capacity of the plasma provides a clinical method for the measurement of acidosis directly in the blood itself. In a series of cases there are now being determined simultaneously, first the alveolar CO_2 ; second, the alkaline reserve of the plasma, according to the electrometric method; third, the CO_2 capacity of the plasma. In the observations so far made the curves obtained by these three methods run parallel. At the same time, the ammonia and acetone body determinations in the urine are being made, to determine their relation to the more direct observations on blood reaction.

Miscellaneous Studies carried on in the Chemical Laboratory, under the Direction of Dr Van Slyke. Mr Ebeling has at last succeeded in the difficult task of obtaining a fistula in the portal vein of a dog so that blood fresh from the active alimentary tract could be drawn at will, and without the use of anesthetic. The results indicate in a beautiful way the manner in which the amino acids are absorbed into the blood during protein digestion, and in turn absorbed from the blood by the tissues. In a given case the amino nitrogen of the portal blood increased 60 per cent after the animal had received a meal of meat, but the jugular blood showed no increase at all, indicating that the amino acids absorbed from the intestine had been entirely removed from circulation during a single passage of the blood through the tissues. These results are in harmony with our previous experimental work on the fate of protein digestion products.

Mr Cullen and Dr Avery have completed their study on the effect of immunization of horses against pneumococci on the relative proportions of the different proteins in the serum. It was found necessary, in order to obtain reliable results, that new methods for the determination of serum globulins and albumin should be devised. The

results obtained have not indicated that through immunization, at least with pneumococci, one or other of the protein fractions is increased over the normal. Whether a similar critical study of the effects obtained by immunization of horses to diphtheria toxin will yield similar results, contrary to those now generally held true, cannot be stated but these observations throw some doubt on present conceptions.

The study of the amino acid content of certain proteins, which Dr Van Slyke and Miss Vinograd began, over a year ago, in collaboration with Professor Osborne of New Haven, has reached a satisfactory conclusion. One point of interest which has finally been settled concerns the content of gliadin, the principal wheat protein, in lysine, one of the amino acids which the work of Osborne and Mendel has shown to be absolutely essential for growth. All work except that from this laboratory had previously indicated that this wheat protein contains no lysine. Nevertheless Osborne and Mendel found that they were able to at least maintain rats in equilibrium with this as their sole protein food. Both laboratories, using refinements of quite different methods, have now ascertained that the wheat protein does contain about one per cent of lysine. Another interesting fact uncovered in this work is that milk albumin contains more lysine than any other protein of either animal or vegetable origin that has yet been analysed. This point is of interest in connection with the growth-stimulating effect of milk albumin noted by Osborne and Mendel. A third point is that in amino acid content the protein of rice is much nearer to the chief animal proteins than are those of other ordinary food grains. This peculiarity in the composition of the rice protein is the probable explanation of the ability of the eastern races which live on it to exist on a very low plane of protein intake.

Study of the Abderhalden reaction, by Miss Vinograd cooperating with Dr Losee of the Lying In Hospital, has been continued. The method employed has consisted in determining the increase in amino-nitrogen in the mixtures as indicating degree of proteolysis. First, proteolytic enzymes occur in measurable amounts in every normal serum. They are by no means characteristic of pregnant sera. Second, such proteo-

lytic enzymes digest not only placenta protein, but other proteins as well. Third, on the average the enzymes in the sera of pregnant women are somewhat more active than those in the sera of non-pregnant women and of normal men. The individual variations, however, in the latter cover nearly, if not quite, as great a range as those of the sera of pregnant women. In certain pathological conditions, moreover, as in pneumonia, apparently the most active digestive action is seen. No evidence, therefore, of the presence of a specific enzyme in the serum of pregnant women has been obtained. The great quantitative variations observed in the amount of the non-specific ferment present in normal and pathological sera, as well as in the sera of pregnant women, indicate that the Abderhalden reaction is unreliable for the diagnosis of pregnancy.

With the assistance of Dr Losee at the Lying In Hospital, studies on the toxemias of pregnancy have been carried out. The most concrete theory concerning these toxemias has been that of Ewing, according to which the toxemias are due to liver insufficiency. The chemical evidence for this was the increase of non-determined nitrogen in the urine, which Ewing attributed to excreted amino acids, which were supposed to have escaped normal catabolism because of the inefficient liver. Direct determinations of the amino acids, as well as the other nitrogenous constituents, not only in the urine but also in the blood, have been made, and the amino acid content in both has been found to be absolutely normal. The results make Ewing's hypothesis untenable. The abnormalities of the urinary nitrogen appear to be, as surmised several years ago by Underhill of New Haven, the abnormalities of hunger, and nothing more.

Studies in Nephritis. Dr McLean has continued his study of kidney function, and has used for this purpose cases of cardiac disease admitted to the Hospital for study and, in addition, a small number of cases suffering from nephritis of various types have been admitted in order that studies may be carried out on them. Dr McLean has continued his study of the ratios between the concentration of chloride and urea in the blood and the rates of excretion of these substances in the urine. The method of estimating the excretory efficiency of the kidney in this manner has been reduced

to a practical basis by Dr McLean, so that the results are expressed in per centage of normal efficiency. The labour of calculation has been reduced to a minimum by devising a slide rule for the purpose, which enables one to perform the otherwise somewhat prolonged calculation in a few seconds. The method for determination of chlorides in small amounts of plasma has been further simplified by Dr McLean so that the results can readily be obtained within a half hour after the blood has been drawn. It is planned to continue this study of nephritis, employing this method in comparison with other methods for determining kidney function.